IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/502,328	Confirmation No. 3294
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Filing or § 371 date	:	19 MAY 2005	
TC/A.U.	:	1609	
Examiner	:	M. MOSHER	
Docket No.	:	CS-118	
Customer No.	:	62,479	

APPENDIX B

Please amend paragraph [0012] in the captioned specification at page 5, as follows:

--The present invention is based, in part, on the discovery that the modified version of Peptide G (CEL-1000) (Asn Gly Gln Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu Ile - SEQ ID NO. 5) obtained by replacing Asn with Asp to form der G (Asp Gly Gln Glu Glu Lys Ala Gly Val Val Ser Thr Gly Leu Ile - SEQ ID NO. ~~7~~ 18), optionally having cyclohexylalanine, D-alanine, acetyl ClAc, or BrAc at position 1, has significantly more potent biological activity than the parent molecule, another form being (Asp Gly Gln Glu Glu Xaa Ala Gly Val Val Ser Thr Gly Leu Ile Gly Gly Gly - SEQ ID NO. 7) optionally having cyclohexylalanine, D-alanine, acetyl ClAc, or BrAc at position 1 and amidation at position 18 where Xaa is an amino acid Val, Leu, Ile, Gly or Ala. The peptides enhance the immune response, particularly the CD4 related (cell mediated) response, independent of being supplied as a conjugated peptides (L.E.A.P.S. ™ constructs) as previously described. Isoaspartic acid is not used since it is not naturally found in

proteins or encoded by the genetic code. Accordingly, the present invention enables the development of compositions useful as a pharmaceutical, adjuvant, immunostimulant or immunomodulator to activate the immune system wherein the compositions may be peptides, non-peptide mimetics or organic molecules selected from aliphatics, carbohydrates, heterocyclics, aromatics, substituted forms and mixtures thereof.--

Please amend paragraph [0056] on page 20 as follows:

--Use of amidation or esterification at carboxyl terminus to reduce sensitivity to carboxylpeptidases of peptide(s).

NGQEEKAGVVSTGLIamide SEQ ID NO. 2

EETVGVSQLEVamide SEQ ID NO. 3 --

Please amend paragraph [0058] on page 21 as follows:

--Changing the amino terminus amino acid to a more stable one N to D or change amino terminus to aspartic acid from unstable asparagines when adjacent to Glycine.

~~derG DGQEEKAGVVSTGLIGGGamide~~

DGQEEXAGVVSTGLIGGGamide SEQ ID NO. 7

DGQEEKAGVVSTGLI SEQ ID NO. 18 --

Please amend paragraph [0059] on page 21 as follows:

--Using acetylated, propionylated, bromo or Chloro of amino terminus amino acid to reduce proteolysis in vivo and thus increase half-life, as shown in following peptides:

~~ClAcDGQEEKAGVVSTGLIGGG-amide~~	
ClAcDGQEEXAGVVSTGLIGGG-amide	SEQ ID NO. 7
~~BrAcDGQEEKAGVVSTGLIGGG-amide~~	
BrAcDGQEEXAGVVSTGLIGGG-amide	SEQ ID NO. 7
ClAcGQEEKAGVVSTGLIGGG-amide	SEQ ID NO. 8
BrAcGQEEKAGVVSTGLIGGG-amide	SEQ ID NO. 8
BrAcEETVGVSQLEVGGGamide	SEQ ID NO. 6
ClAcEETVGVSQLEVGGGamide	SEQ ID NO. 6
~~AcetylDGQEEKAGVVSTGLIGGG-amide~~	
AcetylDGQEEXAGVVSTGLIGGG-amide	SEQ ID NO. 7
AcetylEETVGVSQLEVGGGamide	SEQ ID NO. 8

wherein ClAc represents chloroacetic acid or BrAc for Bromoacetic acid as shown in US 5,066,716 and incorporated herein by reference and acetyl represents a acetylated group added at amino terminus. --

Please amend paragraph [0060] on page 22 as follows:

--Using amino acid analogues (see US Patent 5,736,412) cyclohexylalanine represented by B to reduce potential for rapid proteolysis.

BGQEEKAGVVSTGLIGGGamide	SEQ ID NO. 8

BEETVGVSQLEVGGGamide SEQ ID NO. 6

Or using D-amino acids especially D-Alanine represented by Z, (US Patent 5,736,412) to reduce potential for rapid proteolysis

ZGQEEKAGVVSTGLIGGGamide SEQ ID NO. 8

ZEETVGVSQLEVGGGamide SEQ ID NO. 6 --

Please amend paragraph [0061] bridging pages 22-23 as follows:

--Using substitutions at sites interacting with CD4 that increase binding to CD4 molecules identified in the attached sequence listings. Conserved substitutions with a similar type of amino acid are listed as follows from the groupings. If within the same category but on a different level they are not considered as a conserved substitution.

Non Polar

G, A, (P)

V, L, I

Polar

Neutral

C, M, S, T

N, Q

Acidic

D, E

Basic

K, R (H)

Aromatic

F, W, Y, (H)

such as E137D and/or A140G (V, L, I) and or V142I,L(or G,A) wherein the substitutions in parenthesis are less similar. Additional substitutions are shown below.

NGQEEKAGVVSTGLIGGGamide SEQ ID NO. 5

~~NGQEEKAGVVSTGLIGGGamide~~

~~NGQEEKAGVVSTGLIGGGamide~~

~~NGQEEKAGVVSTGLIGGGamide~~

~~NGQEEKAGVVSTGLIGGGamide~~

~~NGQEEKAGVVSTGLIGGGamide~~

EETVGVSQLEVGGGamide SEQ ID NO. 6

~~EETVGVSQLEVGGGamide~~

~~EETVGVSQLEVGGGamide~~

~~EETVGVSQLEVGGGamide~~

~~EETVGVSQLEVGGGamide~~

~~EETVGVSQLEVGGGamide~~ --

Please amend paragraph [0062] bridging pages 23-24 as follows:

--Using substitutions at sites not interacting with CD4 especially if protease-sensitive especially arginine, lysine or cysteine and making use of other conserved substitution for Lysine

by use of analogues such as substituted ~~episoln~~ epsilon amino (methyl, alkyl) Lysine or hydroxyl-Leucine or Leucine, as in (Asp Gly Gln Glu Glu Xaa Ala Gly Val Val Ser Thr Gly Leu Ile Gly Gly Gly - SEQ ID NO. 9) optionally having cyclohexylalanine, D-alanine, acetyl ClAc, or BrAc at position 1, amidation at position 18, analogues such as substituted epsilon amino (methyl, alkyl), Lysine or hydroxyl-Leucine or Leucine at position 6, where Xaa is an amino acid Val, Leu, Ile, Gly, Ala, Lys or Phe.

~~DGQEEKAGVVSTGLIGGGamide~~	
DGQEEXAGVVSTGLIGGGamide	SEQ ID NO. 9
DGQEEFAGVVSTGLIGGGamide	SEQ ID NO. 10
ClAcGQEEKAGVVSTGLI-amide	SEQ ID NO. 8
BrAcGQEEKAGVVSTGLI-amide	SEQ ID NO. 8
AcetylGQEEKAGVVSTGLI-amide	SEQ ID NO. 8
ZEETVGVSQLEVamide	SEQ ID NO. 3
BEETVGVSQLEVamide	SEQ ID NO. 3
ClAcEETVGVSQLEVamide	SEQ ID NO. 3
BrAcEETVGVSQLEVamide	SEQ ID NO. 3 --

Please amend paragraph [0066] on page 25 as follows:

--Although Humphries et al. (2000 Vaccine 18:2693-7) discloses a 5-aminopentanoic acid replacing four amino acids (LMRK) in their peptide and adds four methylene bridges (-HN-

CH2-CH2-CH2-CH2-CO2), the distal C for the amino function is required. Not the first or α C in the amino acid. Useful replacement of two amino acids for spacers include gamma aminobutyric acid (gaba) or (HN-CH2-CH2-CH2-CO2) and 3 amino propanoic acid (apa) or (HN-CH2-CH2-CO2) replacing 3 or 2 amino acids.

Therefore, GG should be replaced by gaba or apa although other similar substitutions would be within the scope of this inventions as follows:

DGQEEKAapaVVSTGLIGGGamide	SEQ ID NO. 21
DGQEEKAgabaVVSTGLIGGGamide	SEQ ID NO. 21 --

Please amend paragraph [0067] bridging pages 25-26 as follows:

--Examples of other sites where this substitution is illustrated are as follows:

DGQEapaAGVVSTGLIGGGamide	SEQ ID NO. 22
DGQEapaAGGVVSTGLIGGGamide	SEQ ID NO. 20
DGQEgabaAGVVSTGLIGGGamide	SEQ ID NO. 22
DGQEgabaAGGVVSTGLIGGGamide	SEQ ID NO. 20
paEEKAGVVSTGLIGGGamide	SEQ ID NO. 23
apaEEKAGGVVSTGLIGGGamide	SEQ ID NO. 20
abaEEKAGVVSTGLIGGGamide	SEQ ID NO. 23
gabaEEKAGGVVSTGLIGGGamide	SEQ ID NO. 20 --

Please amend paragraph [0072] on page 26 as follows:

--Another critical point for contact with CD4 is an extended sequence to encompass more of the molecule as follows:

NGQEEKAGVVSTGLIqngdwtfqtlv SEQ ID NO. 24. --

Please amend paragraph [0073] on page 26 as follows:

--The residues shown in lower case represent highly variable sites. For example, the isoleucine at 143 and the leucine at 159 in contact with the CD4 phenylalanine as the 43 residue. Then the peptide could be used as the aspartic acid form as follows:

DGQEEKAGVVSTGLI qngdwtfqtv amide SEQ ID NO. 24

or the amino blocked Ac, Pr, ClAc, or BrAc forms:

AcDGQEEKAGVVSTGLIqngdwtfqtlv amide SEQ ID NO. 24

PrDGQEEKAGVVSTGLIqngdwtfqtlv amide SEQ ID NO. 24

ClAcDGQEEKAGVVSTGLIqngdwtfqtlv amide SEQ ID NO. 24

ClAcDGQEEKAGVVSTGLIqngdwtfqtlv amide SEQ ID NO. 24. --

Please amend paragraph [0074] bridging pages 26-27 as follows:

--Since the extended form has the NG sequence which has a tendency to deamidate, a more stable form may have the substitution to DG of:

AcDGQEEKAGVVSTGLIqDgdwtfqtlv amide SEQ ID NO. 25

PrDGQEEKAGVVSTGLIqDgdwtfqtlv amide SEQ ID NO. 25

ClAcDGQEEKAGVVSTGLIqDgdwtfqtlv amide SEQ ID NO. 25

ClAcDGQEEKAGVVSTGLIqDgdwtfqtlv amide SEQ ID NO. 25.--

Please amend paragraph [0075] on page 27 as follows:

--The less hydrophilic α-aminobutanoic acid (Aba) or S is also contemplated:

AcDGQEEKAGVVSTGLIqAAbagdwtfqtlv amide SEQ ID NO. 26

PrDGQEEKAGVVSTGLIqAbagdwtfqtlv amide SEQ ID NO. 26

ClAcDGQEEKAGVVSTGLIqAbagdwtfqtlv amide SEQ ID NO. 26

ClAcDGQEEKAGVVSTGLIqAbagdwtfqtlv amide SEQ ID NO. 26

AcDGQEEKAGVVSTGLIqAbagdwtfqtlv amide SEQ ID NO. 26

PrDGQEEKAGVVSTGLIqAbagdwtfqtlv amide SEQ ID NO. 26

ClAcDGQEEKAGVVSTGLIqAbagdwtfqtlv amide SEQ ID NO. 26

ClAcDGQEEKAGVVSTGLIqsgdwtfqtlv amide SEQ ID NO. 26.--

Please amend paragraph [0076] on page 27 as follows:

--To shorten to reduce cost and size at the amino terminus till the first critical E137 the following constructs may be provided:

AcEKAGVVSTGLIqngdwtfqtlvamide SEQ ID NO. 27

AcEKAGGVVSTGLIqngdwtfqtlvamide SEQ ID NO. 27

PrEKAGVVSTGLIqngdwtfqtlvamide SEQ ID NO. 27

PrEKAGGVVSTGLIqngdwtfqtlvamide SEQ ID NO. 27

ClAcEKAGVVSTGLIqngdwtfqtlvamide SEQ ID NO. 27

ClAcEKAGGVVSTGLIqngdwtfqtlvamide SEQ ID NO. 27

BrAcEKAGVVSTGLIqngdwtfqtlvamide SEQ ID NO. 27

BrAcEKAGGVVSTGLIqngdwtfqtlvamide SEQ ID NO. 27.--

Please amend paragraph [0078] on page 28 as follows:

--The reverse order of amino acids for derG would be as follows can also be contemplated by the present invention:

AcGGGILGTSVVAKEEQGDamide SEQ ID NO. 28

including the D isomer form:

AcGGGILGTSVVAKEEQGDamide SEQ ID NO. 28

AcILGTSVVAKEEQGDamide SEQ ID NO. 28

and successively and sequentially eliminated amino acids down to

AcVAKEamide SEQ ID NO. 29 --